

Oxidative Damage in Neurodegenerative Diseases: Relevance of Dietary Antioxidants

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Abstract

Oxidative stress is induced by an imbalanced redox states, involving either excessive generation of reactive oxygen species (ROS) or dysfunction of the antioxidant system. The brain is one of organs especially vulnerable to the effects of ROS because of its high oxygen demand and its abundance of peroxidation-susceptible lipid cells. Previous studies have demonstrated that oxidative stress plays a central role in a common pathophysiology of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Antioxidant therapy has been suggested for the prevention and treatment of neurodegenerative diseases, although the results with regard to their efficacy of treating neurodegenerative disease have been inconsistent.

Keywords

Oxidative stress, Reactive oxygen species, Neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Antioxidant.

Introduction

Neurodegenerative diseases, as a heterogeneous group of disorders, are characterized by slowly progressive losses of neurons. The etiology of neurodegenerative diseases has not yet been fully elucidated, however increased oxidative stress has been suggested as one of the potential common etiology in various neurodegenerative diseases. Cumulative oxidative stress may induce cellular damage, impairment of the DNA repair system, and mitochondrial dysfunction, all of which have been known as key factors in acceleration of aging process and the development of neurodegenerative disorders. For these reasons, there have been continuing efforts to find the agents that can protect against oxidative damage and potentially treat neurodegenerative diseases. In this review, we focus to discuss the fundamental pathophysiological pathway of oxidative stress to the development of neurodegenerative diseases, especially in Alzheimer's disease (AD) and Parkinson's disease (PD). In addition, we will outline the present knowledge of available evidence in the prevention and treatment of neurodegenerative diseases and future directions for the potential of antioxidant supplementation with enhanced efficacy.

Antioxidant pathway

Cellular ROS levels may be reduced through the defense mechanisms of antioxidant enzymes and small-molecule antioxidants. O_2^- radical can be inactivated by SOD to produce H_2O_2 . Then H_2O_2 may further be removed by the action of glutathione peroxidases, catalase, and peroxiredoxins..

Superoxide dismutase (SOD)

SOD plays a significant role in catalyzing the breakdown of highly reactive O_2^- to less reactive H_2O_2 and oxygen. Cytosolic copper/zinc-SOD (SOD1), mitochondrial manganese SOD (SOD2), and extracellular SOD (SOD3) are three distinct isoforms of SOD that have been identified. SOD1 and SOD2 are mainly involved in the elimination of O_2^- in the cytosol and mitochondria, respectively.

Glutathione (GSH)

GSH, a tripeptide synthesized from glutamate, cysteine, and glycine, exerts protective function of cell survival against oxidative stress. In the brain, *in vivo* GSH is produced by the consecutive actions of two enzymes; γ dipeptide of γ -glutamylcysteine is formed by γ -glutamylcysteine synthetase, using glutamate and cysteine as substrates. And this dipeptide is further combined with glycine by the catalyzing action of glutathionine synthetase to synthesize GSH.

Oxidative stress: excessive accumulation of ROS in a healthy condition, the production of ROS is balanced by various antioxidant systems. Oxidative stress is a condition of imbalance between ROS production and antioxidant defenses, resulting in excessive accumulation of ROS. Oxidative stress may be related to cell membrane damage from lipid peroxidation, changes in protein structure and function due to protein oxidation, and structural damage to DNA.

As the brain is one of the most metabolically active organs in the body, it is vulnerable to oxidative stress particularly because of the following reasons. First, the brain has a high oxygen demand, which constitutes 20% of the body oxygen consumption. Second, the redox-active metals such as iron or copper exist abundantly in the brain and they are actively involved to catalyze ROS formation. Third, the high levels of polyunsaturated fatty acids are found in the brain cell membranes and react as substrates for lipid peroxidation. Fourth, there are relatively low levels of GSH in the brain, which plays a role of endogenous antioxidant in the elimination of ROS.

Oxidative stress in the nervous system

The oxidative stress is a shift towards the pro-oxidant in the pro-oxidant/antioxidant balance that can occur as a result of an increase in

oxidative metabolism. Its increase at the cellular level can come as a consequence of several factors, including exposure to alcohol, cold, medications, trauma, infections, toxins, radiation, strenuous physical activity, and poor diet. Defense against all of these processes is dependent upon the adequacy of various antioxidants that are derived either directly or indirectly from the diet.

Dietary Natural Antioxidants as Upstream Preventive Measure

There are clinical evidences that neurodegenerations can be ameliorated upon dietary intake or supplementary intake of natural antioxidants. Dietary intake contains variety of antioxidants vitamin supplements those play a vital role in neuroprotection in variety of neurological disorders.

These natural antioxidants prevent oxidation of proteins, lipid peroxidations and prevent generation of ROS, thus act as upstream therapeutic barrier to OS.

Results

Possible reasons for little efficacy of antioxidants in treating neurodegenerative diseases

The following explanations may address why the current clinical trials have not yet found the potential antioxidants, which would effectively treat neurodegenerative diseases.

First, antioxidant therapy could not decrease oxidative stress in patients with neurodegenerative diseases potentially due to insufficient dose of antioxidants, unsuitable timing for therapy, or inappropriate duration of treatments. On each related issue, the actual challenge could be how to evaluate the exact effects of antioxidants on the levels of a particular ROS at its proper action sites. It is also important to evaluate the magnitude of therapeutic effects of antioxidants on alterations in levels of a particular ROS at its presumptively proper action sites. In that sense, the development of biomarkers to better assess ROS is critical for the development of novel antioxidant therapeutic approach of neurodegenerative diseases.

Antioxidant System

Cellular levels of ROS are controlled by antioxidant enzymes and small-molecule antioxidants.

Superoxide Dismutase

As major antioxidant enzymes, superoxide dismutases (SODs), play a crucial role in scavenging $O_2^{\bullet-}$. The superoxide dismutase family is specialized in eliminating superoxide anion radicals derived from extracellular stimulants, including ionizing radiation and oxidative insults, together with those primarily produced within the mitochondrial matrix as byproducts of oxygen metabolism through the electron transport chain [100]. Three distinct isoforms of SOD have been identified and characterized in mammals: copper-zinc superoxide dismutase (Cu/ZnSOD; encoded by the *sod1* gene), manganese superoxide dismutase (MnSOD; encoded by the *sod2* gene), and extracellular superoxide dismutase (ECSOD; encoded by the *sod3* gene). These forms of SOD exhibit similar functions, but characteristics of their protein structure, chromosome localization, metal cofactor requirements, gene distribution, and cellular compartmentalization are distinctly different from one another [100].

Glutathione Peroxidases

Glutathione peroxidase is the general name for a family of multiple isozymes that catalyze the reduction of H_2O_2 or organic hydroperoxides to water or corresponding alcohols using reduced glutathione (GSH) as an electron donor ($H_2O_2 + 2GSH \rightarrow GS-SG + 2H_2O$). In mammalian tissues, there are four major selenium-dependent glutathione peroxidases (GPX) and phospholipid hydroperoxide glutathione peroxidase, which incorporates cysteine instead of selenocysteine in the conserved catalytic motif [101]. GPX1 is known to localize primarily in glial cells, in which GP activity is tenfold higher than in neurons [101].

Catalase

Catalase is a ferriheme-containing enzyme that is responsible for the conversion of hydrogen peroxide (but not other peroxides) to water [5]. It is localised in peroxisomes and may also be found in cytoplasm and mitochondria. It has a minor role at low levels of hydrogen peroxide generation but becomes more important at higher levels of hydrogen peroxide production.

Nonenzymatic Antioxidants

GSH

The main antioxidant in CNS, glutathione (GSH), is the most abundant small molecule, nonprotein thiol in cells (present in millimolar concentration in the brain) [102]. It consists of a tripeptide of glutamate, cysteine and glycine characterized by a reactive thiol group and γ -glutamyl bond. Reduced GSH can nonenzymatically act directly with free radicals, notably superoxide radicals, hydroxyl radicals, nitric oxide, and carbon radicals for their removal. GSH peroxidase and GSH reductase can act enzymatically to remove H_2O_2 and maintain GSH in a reduced state [102].

Vitamin E

The role of vitamin E in the central nervous system is not fully understood although it is a lipid soluble molecule with antioxidant function. It appears to neutralize the effect of peroxide and prevent lipid peroxidation in membranes.

Conclusions

The role of oxidative stress in the pathogenesis of neurodegenerative diseases has been well demonstrated in many preclinical and clinical studies. However, the benefit of antioxidant therapy for neurodegenerative diseases is still controversial in human, although the pre-clinical studies have shown promising results. One of reasons for such discrepancy would be that there was no effective measurement of oxidative stress in the brain. Unfortunately, peripheral biomarkers may not necessarily represent oxidative stress in the brain and changes in neuronal function. Therefore, proper central biomarkers for oxidative stress should be identified to detect objective benefits to the brain and find exact therapeutic targets in treating neurodegenerative diseases.

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